

## 4. CAUSES OF COLORECTAL CANCER

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There are many factors that contribute to human cancer. One of the first well-known analyses published by Dool and Peto (1) showed that the major factors were nutrition (35%) and tobacco use (30%). The next mentioned were infection agents (10%), sexual behaviour (7%), industrial occupation (4%), alcohol consumption (3%), environmental pollution (2%) and others. Unfortunately, there are no clear estimates for the causes of colorectal cancer. Lichtenstein estimated that 60% of observed colorectal cancers are due to risky life-style, 35% due to genetic predisposition, and only 5% because of harmful environmental factors (2).

### **Dietary factors**

There is general agreement that the main role in the development of colorectal cancer plays dietary habits. “Diet” covers different types of food, macro- and micronutrients. Despite many studies performed up to date, the knowledge on the role of dietary factors in the etiology of colorectal cancer is inconsistent.

### ***Dietary fibre***

Dietary fibre is one of the most frequently cited macronutrients that may play protective role in colorectal cancer. It was first hypothesized in the 1960, that “the pattern of (non-infectious) colon disease in the Africans ... (was largely due to the role of) natural African diet usually high in their fibre content ... (3)”. Dietary fibre was defined by Trowel in 1976 as “the residue of plant food resistant to hydrolysis by human alimentary enzymes” (4), while “dietary fibre complex” referred to all substances of dietary fibre plus all chemical compounds naturally associated with, and concentrated around these structural polymers. Dietary fibre covers a lot of substances, like cellulose, hemicelluloses, lignin, pectin, gums and mucilages (5). To avoid misclassification of dietary fibre the Association of Official Analytical Chemists and the US Food and Drug Administration updated the definition. Thus, dietary fibre covers all dietary polysaccharides of 10 and more degrees of polymerisation (6).

There are some possible explanations of the protective effect of dietary fibre on the colon and rectum. Fibre in natural way holds water, and thus dilutes carcinogens comprised in food. Water holding by dietary fibre increases faecal volume and in this way

shortens intestinal transit time. This reduces the time carcinogens remain in contact with colon wall, and decreases their carcinogenic effect (7, 8). Moreover, Fleming et al. showed that dietary fibre caused large faecal output, frequent defecations and favourably influenced colonic function (9, 10). There is also evidence, published by McCullough for fibre associated hypertrophy in the colon. McCullough also observed that an increase in the number of crypts per circumference and the number of branched crypts was the effect of dietary fibre (11).

Fibre is relatively resistant to fermentation, however, some components are fermented by gut microflora to produce three main short-chain fatty acids: butyric acid, acetic acid and propionic acid. These have also antycarcinogenic effect by reducing the pH in the content of the large intestine, they alter microbial metabolism and lower ammonia levels (12). Champ recognised butyrate acid as the main nutrient of the colonocyte (13) and Pool-Zobel showed that it may reduce colon cancer risk by suppressing the proliferation of tumour cells and induction of detoxification enzyme glutathione S-transferase (14).

Although, there is growing evidence on protective effect of dietary fibre in animal and human models, the results from epidemiologic studies are inconsistent.

Howe et al. in 1992 presented the results from thirteen case-control studies showing 47% reduction in colorectal cancer risk among those, who consumed at least 26.2 grams of fibre daily (15). Thun in Cancer Prevention Study-II observed protective effect of fibre only among women (RR = 0.62; 95% CI: 0.45–0.86), in men the relationship was not statistically significant (16). Protective effect of fibre was also observed in Health Professionals Follow-up Study (17). However, the results from the Nurses' Health Study (18), the Iowa Women's Health Study (19), the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (20), the Swedish Mammography Screening Cohort (21) and the

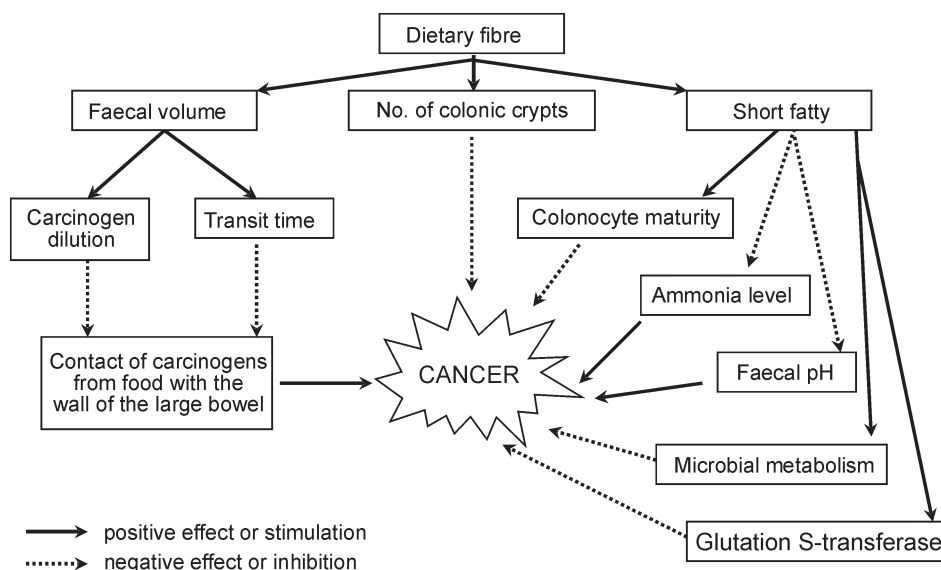


Figure 4.1. The role of dietary fibre in the etiology of colorectal cancer

Breast Cancer Detection Demonstration Project (22) did not confirm statistically significant protective role of fibre in colorectal cancer. Moreover, Boniton-Kopp in the European Cancer Prevention Intervention Study has found, that supplementation of 3.5 g/day of fibre from ispaghula husk increased the risk of developing colon polyps (23).

### ***Fruits and vegetables***

Epidemiologic studies showed that diet, rich in fruits and vegetables, has been associated with reduced risk of colorectal cancer. Fruits and vegetables are natural source of potentially anticarcinogenic substances, like fibre, flavonoids, folic acid, carotenoids, vitamin C and E, selenium, allium compounds, coumarins, dithiolothonies, indole-3-carbinol, isoflavones, isothiocyanates, phytosterols, saponins and protease inhibitors. Some substances are specific for one type or group of fruits or vegetables others are not.

Cruciferous vegetables, such as cauliflower, broccoli, cabbage and brussels sprouts are rich in dithiolothonies and isothiocyanates – substances that have been showed to increase the detoxification enzymes (24).

The allium vegetable group includes onions, leeks and chives. These vegetables are the source of diallyl sulfide and allyl methyl trisulfide, which have been shown to induce enzymatic detoxification systems (25).

Citrus fruits are rich in vitamin C, one of an antioxidant that may protect cell membranes and DNA from oxidative damage. Cumarins are the second active compound characteristic for citrus fruits, and also for some vegetables. Study results showed that cumarins increase the activity of glutathione transferase, one of the detoxification enzymes (26).

Green leafy vegetables contain lutein that has antioxidant activity, and may protect against damage caused by free radicals. It also contains folic acid, deficiency of which may lead to chromosomal damage and reduced methylation of DNA resulting in loss of control of the proper expression of genes (27).

Orange vegetables and some fruits like mango are the part of diet rich in beta carotene. These, like other carotenoids, play protective role as antioxidants, and after change in metabolic pathway into retinol play a role in differentiation of normal epithelium. Beta carotene may further inhibit cell proliferation and may induce increased cell to cell communication. This disturbance leads to loss of control and is common feature of cancer (28, 29).

Analysis made by Steinmetz revealed statistically significant protective effect of fruits and vegetables in the etiology of colorectal cancer in about 75% of published case-control studies (30). Cohort studies provided different results. Giovannucci in 1992 found 47% statistically significant reduction in colorectal cancer polyps (17), however, later analysis of the same study group made by Michaels did not support previous results (31). Some other cohort studies, like the Iowa Women's Health Study (19), the Caerphilly Study (32), the Adventist Health Study (33), the Swedish Mammography Screening Cohort (21) also did not show statistically significant protective effect of vegetables. In the Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective report (34), the authors observed decreased risk with increased intake of vegetables in thirteen of cohort studies, however, only in two of them the results were statistically significant.

In general, the reduction of cancer risk for all cancers, due to high consumption of vegetables and fruits is estimated at 50% (35).

Further well-organised etiological studies are needed to clarify the role of fruits and vegetables consumption in colorectal cancer.

Howe investigated the role of vitamins in metaanalysis of 13 case-control studies and found 15% reduction of colorectal cancer risk among those, whose diet was rich in vitamin C (15). The consumption of at least 157 mg of vitamin C daily decreased by 60% the colorectal cancer risk in the study published by Ferraroni (36). In the Cancer Prevention Study – II Jacobs observed decreased risk of rectal cancer death 10-years after supplementation of vitamin C (37). Although most studies suggested protective effect of vitamin C, not all results were statistically significant.

Similar inconsistent findings come from the studies investigating the role of vitamin E. Though case-control studies showed decreased risk of colorectal cancer the ATBC, the NHS and the HPFS did not support the protective effect (38, 39) the findings from of vitamin E.

Inconsistent were also reports on the role of carotenoids. La Vecchia reported over 50% reduction of the colorectal cancer risk in the group with the upper intake of beta-carotene (40) as opposed to Enger (41) and Slattery (42) who did not confirm these observations. Similarly, intervention trials, such as the Polyp Prevention Study (43), the Australian Polyp Prevention Trial (44) failed to show benefit from supplementation of 20 to 30 mg of beta-carotene. Only in the Antioxidant Polyp Prevention Study among non-drinkers and non-smokers, supplementation of 25 mg of beta-carotene significantly decreased by 44% the risk of polyps development in the bowel.

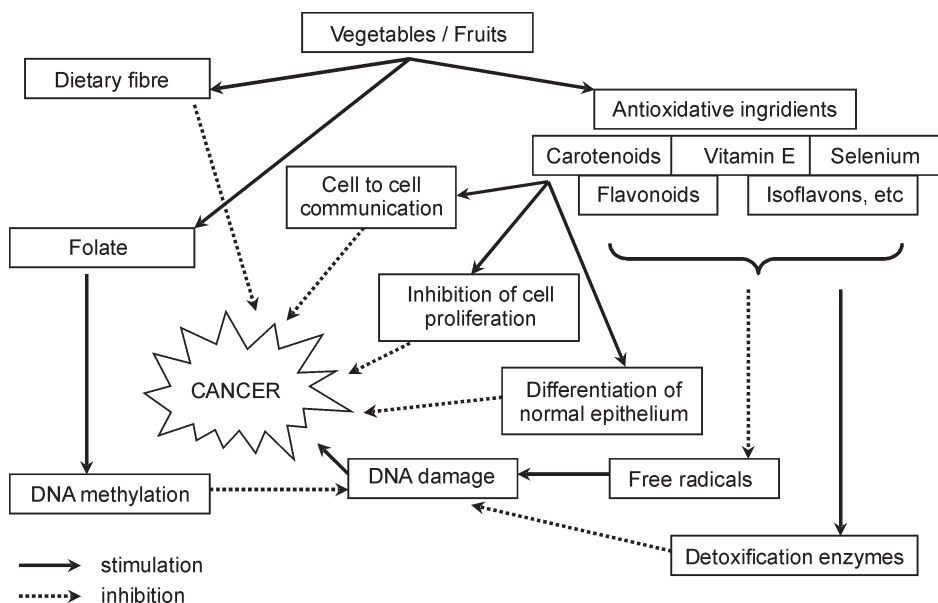


Figure 4.2. The role of eatable plants and their compounds in the etiology of colorectal cancer

## **Folate**

Folate is one of the nutritional factors that play an important role in the pathogenesis of several disorders in humans including cardiovascular disease (45), neural tube and some other congenital defects (46, 47). For the last years, folate was also intensively investigated as a potential actor in the etiology of colorectal cancer. Potential mechanisms of the folate deficiency in the colorectal carcinogenesis are aberrant genomic and site-specific DNA methylation, increased mutagenesis, hyperproliferation and abnormal apoptosis. Folate also modulates DNA methylation and thus determinates gene expression and maintains integrity and stability of DNA (48).

Epidemiologic studies on the role of folic acid in colorectal cancer provided different results, however, they seem to be more consistent than evidence on other micronutrients. Kim assessed the role of folate in cancers of different sites and found about 35% reduction in risk among those, who consumed higher amount of folic acid (49). Giovannucci in the Health Professionals Follow-up Study observed 70% risk reduction in the group of high-folate and methionine and low alcohol intake compared to low-folate and methionine and high alcohol intake (50). Protective effect of folate was also observed in the Nurses' Health Study (51) and the Nutritional Health and Nutrition Examination Survey I (52).

The effect of dietary folic acid also depends on the individual predisposition. Individuals with MTHFR 677 TT genotype with inadequate intake of folate and relatively high consumption of alcohol presented an increased risk of colorectal cancer (53).

To identify the real role of folate in the etiology of colorectal cancer some large, randomised, double blind, placebo-controlled studies are ongoing, however it is not clear, if the results confirm the protective effect of folic acid (54).

## **Meat and dietary fat**

Among others, also meat and dietary fat were considered as potential risk factors for colorectal cancer. Red meat is a source of saturated fatty acids (SFAs). Higher consumption of SFAs increases the production of secondary bile acids, which irritate and damage intestinal mucosa (55). SFAs increase production of diacylglycerols, which disturb appropriate proliferation of enterocytes. Red meat is also a main source of cholesterol. The metabolites of cholesterol (coprostans, cholestans, etc.) show carcinogenic ability. Moreover, red meat is usually cooked at high temperatures, and thus, is a source of PAHs and heterocyclic amines, which are well-known carcinogens (56).

Willet in 1990 observed increased risk of colon cancer among women, who frequently consumed red meat (57). Giovannucci published in 1994 the results of the study showing the increased risk of colorectal cancer among men who consumed at least 5 portions of red meat per week (58). Inversely, the Cancer Prevention Study – II showed no difference in the risk of colorectal cancer death among the highest and the lowest level of meat consumption (59). Lack of relationship was also observed in the Iowa Women Study (60), in the study in Netherlands (61), among Finland men (62), in Norway (63), among women in New York (64), Lutheran Brotherhood (65) and in the Seven Countries Study (66). Up to date there is no clear evidence showing the association between the consumption of red meat and the increasing risk of colorectal cancer. More evident seems to be

relationship between consumption of very-well cooked meat and meat cooked in direct contact with flames that rises the risk of colorectal cancer (67).

Similar inconsistent results were observed in the dietary fat analyses. Although investigations made in eighties and nineties showed proportional relationship between SFAs and colorectal cancer risk (68, 69), and inverse association due to fish oil consumption (70), later observations did not confirm these findings. Giovannucci observed increased risk only for those, who consumed red meat. Poultry and fat from dairy products did not increase the colorectal cancer risk (71). Braga discovered decreased risk only for those, who consumed at least 43 grams of olive oils. Other sources of fat did not significantly influence the risk estimates (72). Fatty acids intake did not rise the colorectal cancer risk in the Kaiser Permanente Medical Care Program (73), in central Sweden (74), and among French-Canadians in Montreal (75). Finally, after analysis of available evidence the Panel of WCRF and AICR stated in the Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective (2007) "There is a limited amount of fairly consistent evidence suggesting that consumption of foods containing animal fat is a cause of colorectal cancer" (76). Hence, the role of red meat and animal fat should be further investigated.

### ***Calcium and dairy products***

Calcium intake may decrease colorectal cancer risk. Possible mechanism explaining the role of calcium is that intracellular calcium directly influences cell growth and apoptosis. Calcium may also bind to bile and fatty acids, preventing them from damaging the intestinal lining (77). There are a lot of epidemiologic studies that investigated the potential role of calcium and dairy products. Analysis of fifteen case-control and eight cohort studies published till 1998 made by Martinez found statistically significant effect of calcium on colorectal cancer risk only in five of case-control and in one cohort study (78). In the ATBC study and in the HPFS study the risk of colorectal cancer in the group of the highest consumption of calcium was decreased by 30 to 40% (79, 80). The protective effect of calcium was also noticed by Cho. The author in the meta-analysis of 10 cohort studies showed significant 14% risk reduction attributed to higher calcium intake (81). The association was not confirmed after analysis of 27 case-controls and 16 cohort studies made by Bergsma-Kadijk (82). Up to date, the available evidence is limited. Study results are inconsistent and some of them did not take into account important potential confounders like fibre, vitamins and genetic predisposition.

Intervention data showed that calcium reduced proliferation in the upper part of the colonic crypt (83), however, these observations were not supported by other authors (84). Calcium may also have effect on the growth of new adenomas (85). The results of randomised controlled trial published by Baron, showed that the supplementation of 1200 mg calcium daily decreased the risk of colorectal adenomas by up to 20% compared to placebo (86). In their summary of the available evidence Potter and Hunter reported: "there is evidence that both dairy foods and supplemental calcium may be inversely associated with (colorectal cancer) risk" (87).

### **Other diet-related factors**

Giovannucci analysed the role of coffee in the meta-analysis of 12 case-control and 5 cohort studies (88). Overall, inverse association was observed, however, there is no clear biological rationale for the causal effect. Hence it would be premature to conclude that the coffee causally diminishes the risk of the development of colorectal cancer.

The risk of colorectal cancer may be increased by the consumption of the higher amount of alcohol. An acetaldehyde, a metabolite of ethanol, is a potent DNA adducts former (89). An alcohol may also inhibit DNA repair by induction of microsomal cytochrome P-450 activity that may result in enhanced level of electrophilic metabolites of procarcinogens, which are not readily detoxified. In addition, chronic consumption of alcohol has been found to depress the activity of O6-methylguanine transferase – an enzyme involved in the repair of carcinogen-induced DNA alkylation (90).

Twenty-four cohort studies on alcoholic drinks and thirteen cohort and forty-one case-control studies on intake of ethanol that were published to 2008 were analysed by the Panel of the WCRF and the AICR. The increased risk of colorectal cancer was observed in eighteen studies on alcoholic drinks, however, only in four of them the results were statistically significant. The meta-analysis of all studies evaluating the role of alcoholic drinks, showed no increase in risk, giving the summary effect of 1.01 per drink over day. The meta-analysis of pure ethanol intake showed that the intake of 10 g ethanol per day significantly increases by 9% the risk of the development of colorectal cancer (91).

### **Physical activity**

There are a lot of studies showing benefit from physical activity in chronic diseases. Most of the published study results showed inverse association between the level of occupational activity, leisure activity, and total activity (92). Hypotheses explaining the role of physical activity pointed at stimulation of colon peristalsis by decreasing the contact time of potential carcinogens in digested mass. Physical activity seems to have the positive effect on the immune system (93). Furthermore, higher physical activity level helps to maintain normal body weight and thereby helps to control appropriate level of insulin and other growth factors (like IGF-I) playing protective role in carcinogenesis, also in colorectal cancer (94, 95).

In the epidemiologic studies, as presented by the Panel of WCRF and AICR, total physical activity was analysed in eleven cohort studies, eight of them showed decreased risk of colorectal cancer, but only three were statistically significant. Additional 12 cohort studies considered occupational physical activity. All of them reported decreased colorectal cancer risk, however, only two of them were statistically significant. Recreational physical activity was evaluated in 24 cohort studies and most of them reported decreased colorectal cancer risk in the group of higher physical activity level (96). Samad published in 2005 a meta-analysis of available evidence on physical activity and the risk of colorectal cancer. The author observed about 20% decrease of the risk among men for occupational and leisure activity (pooled estimates: RR = 0.798; 95% CI: 0.729–0.872; and RR = 0.788; 95% CI: 0.680–0.912, respectively). The presented analysis failed to show positive effect of occupational activity among women, confirmed, however, the



protective role of leisure physical activity (RR = 0.714; 95% CI: 0.574–0.888). Meta-analysis of case-control studies made by the same author showed about 30–50% risk reduction for both genders either for occupational or leisure activity (97). Finally, to summarise the role of physical activity in the etiology of colorectal cancer the Panel of the WCRF and AICR conclude: “the evidence that higher levels of physical activity, within the range studied, protects against colon cancer, is convincing” (96).

## Inflammatory Prostaglandins and Aspirin

Aspirin inhibits the formation of the pro-inflammatory COX-2 enzyme. This enzyme is over expressed in adenomas and some cancers. Inhibition of this enzyme has led to the regression of tumours. Some studies showed that people who take aspirin regularly have a reduced risk of colorectal cancer. Most case-control studies showed the reduction in colorectal cancer risk by 30 to 70% and significant effect was observed for duration of aspirin use longer than 3 years. The analysis of cohort studies showed 22% statistically significant reduction in risk (98). The benefit was observed for the longer duration and higher doses. In the Nurses’ Health Study decreasing trend for colorectal cancer risk with the duration and higher doses of aspirin was also observed. The highest risk reduction (RR = 0.47) was observed for women, who used more than 14 aspirin per week for longer than 10 years (99). Randomized controlled trials, however, did not confirm previous observations. In the Physicians’ Health Study (aspirin dose 325 mg/day) and in the Women’s Health Study (100 mg/day) the authors did not observe protective effect (100, 101). However, among patients with the history of colorectal adenomas the use of NSAIDs significantly reduced the risk of colorectal adenoma (102). The U.S. Preventive Services Task Force (USPSTF), on the basis of the available evidence, “has found good evidence that low-dose aspirin does not lead to a reduction in the incidence of colorectal cancer, fair evidence that higher-dose aspirin and NSAIDs may be associated with a reduction in the incidence of colorectal cancer, and fair evidence that aspirin used over longer periods may be associated with a reduction in the incidence of colorectal cancer.” However, either the U.S. Preventive Services Task Force or the American Cancer Society does not recommend use of aspirin or other NSAID to prevent colorectal cancer because of potential side effects, especially gastrointestinal bleeding (103).

## Environmental factors

Ionising radiation was also considered as a potential risk factor for colorectal cancer. Excess of risk was observed among Japanese atomic bomb survivors, but only for colon not for rectal cancer (104). The follow-up of groups exposed to medical doses did not show consistent results.

Asbestos is another potential risk factor for colorectal cancer. Morgan published a review of the published papers on asbestos and the risk of death due to gastrointestinal cancer. The author observed elevated risk of death from oesophageal and stomach cancer, however, the colorectal cancer risk, although slightly increased, was not statistically significant (105). Kang observed the increased risk of death among workers exposed to



high level of asbestos, however the author also stated that the magnitude of the effect was very small (106).

## Other possible risk factors

Other possible risk factors contributing to the development of colorectal cancer are inflammatory bowel disease (107), Crohn's disease (108), cholecystectomy (109), use of laxative (110) and hormone replacement therapy. There is evidence that estrogen receptor hypermethylation increases with age and that is central feature of colon cancer (111). Hormone replacement therapy may complement the declining endogenous estrogens level and thus reduce the probability that the estrogen receptor gene will be silenced by methylation (112). In human epidemiologic studies some investigators reported an approximate halving the risk of colorectal cancer with the use of hormone replacement therapy (113, 114).

The knowledge on colorectal cancer risk factors is inconsistent and requires further investigations. There are probably others risk factors except those mentioned above that contribute to the development of colorectal cancer. Nowadays, the large ongoing studies are trying to explain the real role of dietary factors in the etiology of this disease and probably more, good quality studies will be required to confirm discussed relationships.

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